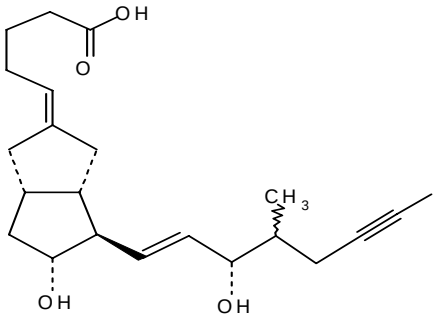
SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Ventavis. For information on changes after approval please refer to module 8.

1. Introduction

Ventavis contains iloprost, (ZK 36374; 5-{(E)-(1S, 5S, 6R, 7R)-7-hydroxy-6-[(E)-(3S, 4RS)-3-hydroxy-4-methyl-1-octen-6-inyl]-bi-cyclo[3.3.0]octan-3-ylidene}pentanoic acid), a chemically stable synthetic analogue of prostacyclin PGI2. There are 6 stereogenic centers in the molecule. Iloprost is an approximately equal mixture of two diastereoisomers with the 4-methyl group the hydroxy methyl octenyl in either the R or the S position; the other 5 stereogenic centers are pure R or S.



An intravenous formulation of iloprost is marketed under the trade name Ilomedine in several European member states and was authorised through national procedures. The approved indications include the treatment of thromboangiitis obliterans with ulcers or rest pain, severe inoperable peripheral arterial occlusive disease stages III-IV, and severe Raynaud's phenomenon.

VENTAVIS 10 µg/ml nebuliser solution in ampoules containing 2 ml of solution (i.e. 20µg iloprost) is intended for administration via the inhalation route with a nebuliser.
Pulmonary Arterial Hypertension (PAH) can occur without apparent cause (Primary Pulmonary Hypertension)(PPH) or be secondary to systemic disease, such as systemic sclerosis, CREST syndrome, mixed connective tissue disease (MCTD), HIV infection or be induced by drugs/toxins. Pulmonary hypertension may also be caused by chronic thromboembolic occlusions of the pulmonary arteries.
The pathogenesis involves vasoconstriction, vascular remodelling, and thrombosis *in situ* resulting in a progressive increase in pulmonary vascular resistances leading to increase pulmonary hypertension. Death is most closely associated with an increase in pulmonary artery pressure and right atrial pressure and a decrease in cardiac output due to failure of the right side of the heart. Pulmonary hypertension is clinically defined as a mean pulmonary arterial pressure of more than 25 mmHg at rest or 30 mmHg during exercise.

The incidence of PPH amounts to 1 to 2 cases per million individuals per year. PPH and the following forms of SPH: connective tissue disease pulmonary hypertension, drug-induced pulmonary hypertension, portopulmonary hypertension, pulmonary hypertension associated with congenital heart disease and chronic thromboembolic pulmonary hypertension are estimated to be affecting approximately 2.2 per 10,000 persons in the European Community.

At the present time, the conventional therapy for patients with primary or secondary pulmonary arterial hypertension includes vasodilators, such as high doses of calcium-channel blockers, anticoagulants and oxygen. Epoprostenol (prostacyclin) delivered via a portable pump system into an in dwelling central vein catheter has been shown to improve hemodynamic parameters and exercise capacity in patients with both PPH and secondary PAH (functional class III and IV), and it has been

shown to improve survival in patients with severe conditions. Pharmacological tolerance with need for dose increments during long-term treatment is commonly observed.

The severity of pulmonary hypertension is classified according to the WHO functional assessment 1998 WHO World Symposium (modified after the NYHA functional assessment). Functional class is a predictor of survival. Patients who are in functional class II and III have a mean survival of 3.5 years compared with a mean survival of 6 months for those who are in functional class IV.

Ventavis is indicated for treatment of patients with PPH, classified as NYHA functional class III, to improve exercise capacity and symptoms.

The recommended dose regimen of Ventavis is 2.5 micrograms or 5.0 micrograms of inhaled iloprost (as delivered at the mouthpiece of the nebuliser). The dose per inhalation session should be administered 6 to 9 times per day according to the individual need and tolerability. The duration of treatment depends on clinical status and is left to physician's discretion. Ventavis should only be initiated and monitored by a physician experienced in the treatment of pulmonary hypertension.

2. Part II: Chemical, Pharmaceutical And Biological Aspects

Composition

Ventavis is an aqueous, clear, sterile, ready to use nebuliser solution for inhalation. It is an isotonic solution in dilute ethanol with a pH close to 8.0. Ventavis contains 10µg/ml of the active substance, iloprost, (as trometamol salt). 2 ml of the solution are supplied in single glass (type I) ampoules of 3 ml.

Active substance

Iloprost (INN), is a synthetic analogue of the natural prostacyclin PGI_2 , IUPAC name: 5-{(E)-(1S,5S,6R,7R)-7-Hydroxy-6-[(E)-(3S,4RS)-3-hydroxy-4-methyl-1-octen-6-ynyl]-bicyclo[3.3.0]oct-3-ylidene}-pentanoic acid . Iloprost is an oily substance, very slightly soluble in water. Due to its chiral centers, iloprost is an optically active diastereoisomeric mixture which also exhibits geometric (-Z- E-) isomerism.

The synthesis of Iloprost can be divided into three parts:
- (1) the manufacture of the basic backbone bicyclo-octane (BCO).
- (2) Addition of the side chain.
- (3) Modification of the side chains.

Particular attention is paid to isomeric/stereochemical control and the process involves optical resolution by preparative HPLC on a chirally-modified substrate, in order to obtain desired enantiomers. Chromatography is necessary at a number of stages and relevant diastereoisomers are separated by HPLC during the process.

Iloprost possesses 6 asymmetrical carbon atoms of which 5 are common with the those in the natural prostacyclin. The configuration of the molecule is therefore namely 8S, 9S, 11R, 12S and 15S. The methyl group at C16 causes two isomers to occur: 16R and 16S. Consequently, iloprost consists of two optically active diastereoisomers. Iloprost also contains two defined configurations of carbon-carbon double bonds, 5E and 13E - this stereo-specific formation is common in prostaglandin chemistry.
The separated methyl diastereoisomers E(16S) and E(16R) -iloprost are obtained as crystals and the isomer ratio has been determined. This ratio is [45/55] of [E(16S) / E(16R)] and has been shown to be unchanged since the pre-clinical and clinical development program began. Moreover, it was shown that there was no significant difference in the pharmacokinetic parameters of the E (16R)-iloprost, E (16S)-iloprost and diastereoisomer mixture. Further data (i.v. infusion in dogs) demonstrated that the diastereoisomers do not undergo inter-conversion *in vivo*.

The structure of Iloprost has been confirmed by IR, NMR, SM and X-ray spectroscopy as well as mechanistic arguments derived from the synthetic route. Solid state variables related to bioavailability are not relevant as the substance is administered in solution.

Active substance specification

The specification includes tests for identity, specific optical rotation, assay determination of identitifed and unidentified related substances by HPLC; Z- isomers are quantified separately. Levels of those related impurities, which are mentioned in the specification are qualified by animal toxicology studies. The isomer ratio E(16R):E(16S) is also checked.
The level of residual solvents and catalysts are adequately discussed and are acceptable taking into account the small therapeutic quantities in which iloprost is administered. Batch analytical data indicate satisfactory compliance with the agreed specification and uniformity from batch to batch.

Stability of the active substance

Prostaglandins in general are unstable substances. The stability of iloprost has been studied under forced degradation conditions, and for three batches, stability studies have been carried out in long term (at –18°C for three years) and under accelerated conditions (at +6°C / uncontrolled RH for 6 months and at +25°C / 60% RH for 1month). The samples used for long term and accelerated stability studies were stored in glass vials .

These stressing conditions show that iloprost is sensitive to temperature, light and acid conditions as expected, and that the substance is not sensitive to alkalis and oxygen.
15ß-Hydroxy-iloprost, 15-Oxo-iloprost, iloprost -ethyl- and iloprost-isopropyl ester and the dimeric esters iloprost-11-iloprost ester and iloprost-15-iloprost ester were identified as the main decomposition products.
After 36 months storage at -18 °C the samples of iloprost show a time dependent tendency of a decrease of the content of iloprost accompanied by a minor increase of the main decomposition products iloprost -11-iloprost ester and iloprost -15-iloprost ester. After longer storage periods, the decrease does not continue. Changes in other parameters such as appearance, isomer ratio E(4R)/E(4S) and Z-isomers are not time-dependent .
At higher temperatures, +6 °C and +25 °C/60 % RH, iloprost decomposes significantly. The oily substance crystallizes and gets turbid, the amount of decomposition products increases, particularly the inner iloprost esters iloprost-11-iloprost ester and iloprost -15-iloprost ester and the content of iloprost decreases, both below the specification limits. Isomer ratio and the amount of Z-isomer remain unchanged however.

It is clear that iloprost is an unstable substance and must be stored with care. A three years shelf- life with a re-test period of one year is acceptable when the active substance is stored sealed at –18° C and protected from light. (For stability of finished product: see below).

Other ingredients

The ingredients of the formulation are defined in the SPC. All are of PhEur standard and there are no significant risks in relation to TSE.

Product development and finished product

Product Development

Development of the formulation is simple and is governed by the need to produce a sterile, isotonic solution suitable for nebulisation without the need for any extraneous excipients, which may have an adverse effect when given by the pulmonary route. The product can withstand terminal heat sterilisation.

In the overall development history, it should be noted that clinical trials were not performed with this product as intended for marketing. They were performed with solutions prepared from another, intravenous, product already-authorised, containing 20 µg iloprost / ml, diluted with isotonic saline (1:1) and nebulised for pulmonary administration. The same amount of active substance would be administered in both cases; differences in safety profiles arising from different formulations and excipients used were regarded as not significant.

Use with inhalation devices

In vitro performance tests were performed with the product nebulised with different inhalation devices. The goal of those studies was to evaluate the performance characteristics of the different inhalation devices and to compare those with the device used in the clinical trials. On the basis of these investigations, relevant information has been included in the SPC to indicate which inhalation devices can be used since they met the experimental parameters.

Manufacture of the Product

In summary, the manufacturing process is: dissolution of trometamol and sodium chloride in water for injection, a dissolution of Iloprost in ethanol and a mixing of the 2 phases, followed by a pH adjustment, a volume adjustment, and a filtration on a 0.22 µm filter. After filling of the solution, the ampoules are sealed and sterilized at 121°C for 20 min, and visually checked. Satisfactory in process controls are carried out: bulk pH, integrity of the filter membrane, yield, filled volume etc.

Concerning the validation of the manufacturing process, the results are those of the validation of the intravenous solution, which is more concentrated. They indicate the good stability of the drug in ethanolic or unbuffered solution during 24 hours at room temperature. There are no adsorption losses of the drug during the process, and there is no significant degradation after one or two sterilisation cycles. The validation studies also show that the bulk solution after filtration is essentially free of microorganisms prior to terminal sterilisation.

Product Specification

At release, the product is examined for appearance of the solution, pH value, extractable volume, identification of iloprost and trometamol, sterility. The assay of iloprost and determination of impurities are performed by validated HPLC methods.
Batch analytical data show good product uniformity.
Identical specifications are applied at release and end of shelflife.
The limits for degradation products are based on results generated in the stability studies.

Stability of the product

Stability studies have been carried out on three batches under ICH conditions. The batches meet the specification after 6 months' storage at + 40 °C/75% RH and after 18 months‘ storage at + 25 °C/60% RH and 30 °C/70% RH.
All three batches exhibit no significant changes on storage compared to the results at start..
In general, the results support the shelf-life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The synthetic control and purity of iloprost active substance has been well-described, in particular the isomeric control during synthesis and general purity aspects as reflected in the active substance specification. As expected, this prostanoid is intrinsically unstable and must be stored frozen at low temperature. Furthermore, the chosen manufacturing process and the specification for the finished product will allow a good quality of this medicinal product. Stability of the product has also been shown to be satisfactory when due allowance is made for the unstable nature of the active substance.
The compatibility of this product with commercially-available nebulisation devices available in the EU is addressed in the Clinical section below and in the SPC.
In general, the information provided in the Chemical and Pharmaceutical documentation suggests this is a product that should have satisfactory and uniform quality characteristics from batch to batch.

At the time of the opinion, there was an unresolved minor pharmaceutical issue on the validation of the manufacturing process having no impact on the benefit/risk balance of the product. The applicant committed to resolve this by means of a post-opinion Follow-Up Measure within an agreed timeframe.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

In vitro studies

Iloprost is a raceme mixture of E-4R- and E-4S- diastereoisomers; it binds with high affinity both to prostacyclin (IP-) receptors and to the EP1-subtype of prostaglandin E receptors. Binding of iloprost to IP-receptors activates adenylate cyclase and increases intracellular cyclic AMP concentration. This iloprost-induced rise of cAMP alters gene expression of IP-receptors.
Human pulmonary vascular tissue was shown to respond to iloprost with vasorelaxation and this was also seen, but to a lesser extent, in human pulmonary artery preparations from patients with pulmonary hypertension. However, in isolated normoxic-perfused rat lung iloprost did not lower pulmonary artery pressure, but it potently inhibited hypoxia-induced vasoconstriction. These differences are presumably due to variations of the expression of functional IP-receptors.
In vitro, iloprost was shown to dilate blood vessels from a number of species pre-contracted with a variety of vasoconstrictors (histamine, noradrenaline, angiotensine II). The E-4S-isomer of iloprost has a potency *in vitro* of approximately 3 times that of iloprost, whereas the E-4R-isomer is about 4 times less potent than iloprost.
Iloprost is a common pathway inhibitor of platelet activation, acting via binding to platelet IP-receptors and has been shown to inhibit aggregation *in vitro* of platelets from several species (human, dog, cat, rat, cattle and monkey), with IC_{50} concentrations ranging from 0.06 ng/ml (1.6×10^{-10} M in humans) to 4.3 ng/ml (1.2×10^{-8} M in monkeys). With regard to inhibition of platelet aggregation in human platelet-rich-plasma (PRP), iloprost has a potency of approximately twice that of prostacyclin and 17 times that of PGE_1. Similarly to the vascular effects, the E-4S-isomer is approximately 1.5 to 2 times as potent as iloprost in inhibiting platelet aggregation and the E-4R-isomer 4 to 7 times less potent.
Further, *in vitro*, iloprost was shown to reduce the LPS-induced up-regulation of pro-inflammatory tumour necrosis factor and in human and animal monocytic cells and monocytic/macrophage cell lines.

In vivo studies

For technical reasons, most *in vivo* data have been obtained using intravenous administration of iloprost. The summary of pharmacodynamic studies performed by the intravenous route in support of the Ilomedin application is presented. There are no pharmacodynamic animal studies using inhaled iloprost, since the intravenous and oral studies have demonstrated that its inhibitory action on platelet aggregation and vasodilatation is due to iloprost binding to the PGI_2 receptors.
The pharmacodynamic properties of iloprost are those expected for a prostacyclin analogue.
Iloprost has shown vasodilatory effect on pulmonary and systemic blood vessels in various animal species, with variations presumably depending on the distribution of functional IP-receptors. In pulmonary hypertension animal models, iloprost treatment leads *in vivo* to an improvement or normalisation of pulmonary haemodynamics by reduction in vascular resistance and consequently in arterial blood pressure. Leukocyte adhesion to damaged endothelium *in vivo*, and leukocyte accumulation in tissue following injury is reduced by iloprost. Iloprost has shown platelet antiaggregatory and antithrombotic effects, favorable effects on microvascular perfusion and microvascular integrity and inhibition of leukocyte-vessel wall interactions. Iloprost is characterized as a common pathway inhibitor of aggregation of human platelets and from varying animal species, probably by increasing the endogenous fibrinolytic potential *in vivo*. Moreover, iloprost is able to inhibit the procoagulant activity of monocytic cells stimulated with LPS, TNFα or IL-1β.
Continuous administration of iloprost does not seem to result in loss of vasodilator response, although loss of the platelet inhibitory effect of the compound on continuous exposure has been shown. With

regard to antithrombotic effects, somewhat reduced efficacy to platelet inhibition was seen following continuous intravenous infusion for 9 days. Development of tachyphylaxis to the anti-platelet effect can be avoided by discontinuous treatment.

Pharmacodynamic drug interactions

Iloprost has been tested in combination with a number of other cardiovascular drugs. No major unexpected interactions were found.
In animal studies, combinations of iloprost with other vasodilator principles resulted in most cases in sub-additive or additive systemic blood pressure lowering effects. An exception to this was the markedly super-additive effect on blood pressure seen with the combination of a moderately hypotensive dose of an ACE inhibitor (captopril) with a non-hypotensive dose of iloprost. Pretreatment with dexamethasone attenuated the blood pressure lowering effect of iloprost, but had no influence on the antiplatelet effect. Iloprost did not influence the positive inotropic response to the cardiac glycoside ouabain.
With regard to the effects on platelets and coagulation, synergistic inhibition of platelet aggregation *in vitro* was seen for combinations of iloprost with acetylsalicylic acid, NO-donors or the phosphodiesterase inhibitor piroximone. Combination with anticoagulants such as heparin may result in increased bleeding time. Under certain conditions, combination of iloprost with tissue plasminogen activator has been shown to reduce plasma t-PA concentration, and may therefore reduce thrombolytic efficacy.

General and safety pharmacology programme

Effects of iloprost have been studied on the central and autonomic nervous system and on the cardiac, respiratory, renal, gastrointestinal and female reproductive systems. The results of these studies performed in animals and *in vitro* can be summarized as follows:

- Iloprost showed limited direct positive inotropic or chronotropic effects in cardiac tissue *in vitro* that probably do not influence its cardiovascular effects *in vivo*. The compound improved the circulatory shock provoked by ovalbumin injection in cats, which had previously undergone passive pre-sensitisation.
- No effects on cardiac action potential, no pro-arrhythmic effects *in vitro* and *in vivo* in rats and mice.
- Symptoms of depression (probably due to exaggerated pharmacological effects, e.g. peripheral vasodilatation and hypotension) and, at high doses, of CNS/autonomic stimulation in rats.
- No deleterious effects on respiratory function *in vitro* and *in vivo* in rabbits.
- Decreased urine flow and sodium excretion at hypotensive doses, which is rapidly reversed on cessation of administration in rats.
- Contractile effects on isolated ileum, little effect or decreased motility and antidiarrhoeic/anti-enteropooling effects (depending on model system) *in vivo* in rats and rabbits.
- Uterine contractile (guinea-pig) or biphasic (human) effects *in vitro*. No effect on uterine pressure and motility *in vivo* in anaesthetized rabbits, induction of abortion at near-lethal doses in guinea pigs.

None of the studies on the effects of iloprost in various organ systems indicate a potential of the compound to induce serious adverse effects in the therapeutic dose range.

Pharmacokinetics

Preclinical pharmacokinetic data are mainly based on conventional routes of drug administration, i.e. the intravenous, oral and subcutaneous routes. The pharmacokinetics of pharmacological to subtoxic doses of iloprost was studied in rodents (rat, mouse and rabbit) and non-rodent species (cat, dog and cynomolgus monkey).
The pharmacokinetics of iloprost is characterized by very rapid and presumably complete absorption from the gastrointestinal tract in the rat, dog and cynomolgus monkey. The bioavailability of orally administered drug was approximately 10% of the dose in all species studied (rat, mouse, dog, monkey), including humans. The disposition half-life of unchanged iloprost was below 15 min in the rat, monkey and dog and about 0.5 h in the cat and in humans.

Following administration, it rapidly distributes into organs and tissues (with minor passage across the blood-brain and blood-placenta barriers) and is extensively biotransformed prior to excretion (preferentially via the kidney).
The pharmacokinetics of iloprost was further studied after inhalative daily administration in rats. Iloprost serum concentrations rapidly increased reaching C_{max} 1 to2 hours after start of inhalation. At the doses used (3.6 to 43.7 µg/kg), average C_{max} and AUC_{0-t} were several times those observed in men given 5 µg iloprost by inhalation. No important differences were observed in C_{max} and AUC_{0-t} between sexes and between treatment days. The systemic exposure increased sub-proportionally with increasing the dose (3.6 to 43.7 µg/kg) and proportionally with prolonging the inhalation period (from 135 to 240 min).
Iloprost isomers exhibited a similar pharmacokinetic behaviour in rats. No conversion of 4R to 4S iloprost (and *vice versa*) occurred. The relevant half-life of labelled compounds in plasma was similar (0.7 h) in all animal species studied (rat, monkey, dog, mouse and cat). Distribution of ^{3}H-active substances into tissues and organs was very rapid. However, concentrations were very low except for the liver, kidneys, muscle and stomach. In rabbit foetuses, concentrations of labelled compounds were 1/200 as compared to maternal plasma.
Iloprost was totally metabolised in all species studied and the biodegradation products were excreted mainly with the urine. Main biotransformation pathways of iloprost were β-oxidation of the upper side-chain and hydroxylation at position 17.

Toxicology

Preclinical safety tests included intravenous, subcutaneous and oral studies in rodent and non-rodent species. Since the systemic iloprost exposure after parenteral and oral administration exceeds the therapeutic inhalative dose levels in humans, it was considered that specific studies of its inhalatory toxicity are not crucial. Complementary studies were carried out primarily to ensure the comparability of the effects after inhalation to those observed after iloprost oral or intravenous administration ("bridging" studies). All studies were done according to GLP rules.

Single dose toxicity

Single dose toxicity studies were carried out in three rodent species (mouse, rat, and rabbit) and in monkey, by oral or intravenous administration. Any acute inhalation toxicity study could not be carried out because of technical impossibility to exceed 0,345 µg of Iloprost per air liter, a concentration that does not induce any adverse effect in the animal, even after chronic treatment.

Design and results (LD_{50}) of systemic toxicity tests with a single intravenous (i.v.) and intragastric (i.g.) administration:

Species	Dose (mg/kg)	Number of animals per dose and sex	Route of administration	LD_{50}-values and 95% confidence limits (mg/kg)
MOUSE	125 to 250	10M	i.v.	201 (179-244)
	125 to 300	10F	i.v.	204 (168-247)
Rat	50 to 200	5M/5F	i.v.	119 (85-164)
	65 to 200	5M/5F	i.v.	M: 128 (92-216)
				F: 144 (116-201)
Rabbit	2.5 to 25	3M/3F	i.v.	9.8 (5.5-16.0)
Monkey	2.5 and 5	1M/1F	i.v.	> 5
Mouse	40 to 100	3M	i.g.	> 100
Rat	40 to 100	3M	i.g.	> 100

M = male, F = female, i.v. = intravenous, i.g; = intragastric

The values of LD_{50} are much higher than the human therapeutic doses corresponding to six to nine administrations per inhalation between five and ten minutes of 2,5 or 5 µg of Iloprost. These human therapeutic doses correspond to an intake of 30 to 45 µg/day of Iloprost i.e 0,5 to 0,75 µg/kg/day.

Clinical symptoms, which appeared right from low dose, are common to all species. Most of the clinical symptoms at high dose such as apathy, changes of posture, redness of the skin and the mucous membranes can be attributed to an exaggerated pharmacological activity of the compound (hypotensive and hemodynamic effects). The necrosis of the tail observed in surviving animals sacrificed at the end of the study is most probably due to local irritating properties of Iloprost at the high concentrations required for these studies.
Based on the administered doses and the LD_{50} obtained, in spite of the absence of animal data on the levels of exposure after inhalation, no special hazard is expected after the single administration of iloprost via inhalation.

Repeated dose toxicity

Subacute toxicity studies were performed by the oral route in rats and monkeys (Macaca fascicularis) by repeated intragastric administration of Iloprost solution, and by the intravenous route in rats and monkeys (Macaca fascicularis) with repeated intravenous infusion over 3 hours and continuous intravenous infusion of Iloprost.

For the assessment of local and systemic toxicity of iloprost after inhalative administration, Wistar rats were exposed by inhalation to three target concentrations generated by nebulization of iloprost 10 µg/mL formulation (corresponding to target doses of 0.9, 3.6 and 10.8 µg/kg) and two concentrations of iloprost 20 µg/mL (corresponding to target doses of 0.9 and 24.6 µg/kg) daily for 135 minutes on seven days a week for 28 days. The selection of dose levels is based on multiples of the maximum human therapeutic dose level of 0.9 µg/kg/day. The duration of exposure was selected to simulate the clinical treatment regimen of a maximum of 9 exposure cycles of 15 minutes duration daily.
After 4 weeks inhalation in the rat with an amount considered as maximum from a technical point of view, there was no difference in toxic effect (clinical, biological and histological) between the different concentrations of Iloprost during or after the exposure. After histological examination of the respiratory tract, no sign of local irritation was observed.

Summary of the relevant doses for evaluation of systemic tolerance of iloprost after inhalation or i.v. administration (subacute toxicity).

Treatment regimen Species	**Doses which were tolerated without symptoms or with minor effects**		**Multiple of the intended human dose[1] on the basis of**	
	mg/kg/day	**µg/kg/min**	**mg/kg/day**	**µg/kg/min**
Inhalation for 135 minutes/day over 28 days				
Rat	0.0226	0.167	25	16.7
i.v. infusion over 3 hours/day (10-11 treatment days)				
Rat	0.2	1.11	222	111
Monkey	0.002	0.011	2.2	1.1
Continuous i.v. infusion over 28 days				
Rat	0.2 (*124*)	0.139 (*0.09*)	222 (*138*)	13.9 (*9*)
Monkey[2]	0.02 (*12.4*)	0.014 (*0.009*)	22.2 (*13.8*)	1.4 (*1*)

[1] Human therapeutic dose per inhalation session of 10 minutes: 5 µg/patient of 50 kg = 0.1 µg/kg/10 min session = 0.01 µg/kg/min. For 9 sessions of 10 minutes/day the total dose is 0.9 µg/kg.

All iloprost related alterations found in the subacute toxicity studies after different routes of administration in rodents and non-rodents are mainly attributed to the hemodynamic properties of iloprost. At very high exposure levels, the hemodynamic changes led to the death of experimental animals, however direct organ toxicity was not observed. Considering a single inhalation dose of 5 µg/patient (= 0.1 µg/kg for a patient of 50 kg body weight for 10 minutes) administered up to 9 times a day as the intended mode of application, it can be concluded that on the basis of total administered dose/day and on the basis of dose/kg/min, many times higher dosages of iloprost were tolerated in rats after inhalation than after administration via the intravenous or oral routes of administration. In

monkeys, which were more sensitive to iloprost, the doses that were tolerated without or with minor symptoms after parenteral and oral administration were in the same range or slightly above the dose levels of human inhalative therapeutic treatment.

Chronic toxicity studies were carried out in rats and dogs by intravenous or subcutaneous continuous infusion or oral administration of Iloprost over 6 months. A chronic inhalation toxicity study was conducted in rats over 26 weeks (periods of 135 or 240 min/day).

Continuous infusion of Iloprost up to the highest dose of 347 ng/kg/min (0.5 mg/kg/day) over 26 weeks in rats did not produce any organ-toxic effect, but slight effects related to the pharmacological profile of the compound. The mean plasma levels of Iloprost at the highest dose were for females 3.5 ng/ml and for males 5.0 ng/ml. In dogs, continuous s.c. infusion of iloprost up to the highest dose of 67 ng/kg/min (0.097 mg/kg/day) over 26 weeks did not produce any organ-toxic damage, though adverse effects related to gastrointestinal motility could be observed transiently from the mid-dose (33-34 ng/kg/min; 0.049 mg/kg/day) leading to mean plasma levels of 0.9 ng/ml onwards. The mean plasma levels of Iloprost at the highest dose were 1.6 and 2.1 ng/ml in female and male animals, respectively.

The daily inhalative administration of a nebulizing solution of Iloprost at a concentration of 20 µg/ml over 26 weeks in rats, with a maximum technically achievable aerosol concentration which led to a maximum achievable dose of 48.7 µg/kg body weight, did not cause adverse effects. The technically possible maximum amount (0,4 µg/l air) corresponding to 0,203 µg/kg/min (human: 0,01 µg/kg/min) is approximately 200 times the human amount.
The systemic burden in the male rats at the highest dose amounted to C_{max} values of approx. 2.1 ng/ml and in female rats to 2.9 ng/ml and average AUC value of 372 ngxmin/ml.
The exposure obtained is 13-18 times and 127 times higher, respectively in terms of C_{max} and of AUC, than that obtained in humans during a single inhalation session of 10 min.

Table : **Summary of the relevant doses, plasma levels or AUCs for evaluation of systemic tolerance of iloprost after inhalation, continuous i.v. or s.c. infusion or oral administration**

Species / treatment regime	Doses or plasma levels which were tolerated without or with minor effects			Multiples of the human exposure based on				Ref. Report
	Doses of iloprost	Mean iloprost plasma levels (pg/ml)	AUC (pg*h/ml)	dose[1]	plasma levels[2]	AUC[3]	max. daily expos.[4]	
Repeated dose toxicity studies								
Rat, inhalation, 4 weeks	22.6 µg/kg/135min (=167 ng/kg/min)	M + F: 677	1414	17	4.3	29	3.2	B784
Rat, inhalation, 26 weeks	48.7 µg/kg/4h (=203 ng/kg/min)	M + F: 2099	8396	20	13	171	19	A05405
Rat, contin. i.v. infusion, 26 weeks	347 ng/kg/min (500 µg/kg/day)	M + F: 4399	105576	35	28	2155	239	7442
Rat, iloprost clathrate, diet, 27-28 weeks	ca. 1.5 mg/kg/day	M + F: 1260	30240	--	8	617	69	AB90
Dog continuous s.c. infusion over 26 weeks	67 ng/kg/min (97 µg/kg/day)	M + F: 1900	45600	7	12	931	103	7949
Dog, iloprost clathrate, oral, 53 weeks	2 x 75 µg/kg/day	M +F: 940	5584	--	5.9	114	13	A693

[1] therapeutic dose per inhalation session = ca. 0.01 µg/kg/min for a patient of 50 kg body weight
[2] human plasma level at a therapeutic dose of 5 µg/patient/session = 158 ± 70 pg/mL (c_{max})
[3] human AUC at therapeutic dose of 5 µg/patient/inhalation session = 49 ± 34 pg*h/ml
[4] calculated for 9 inhalation sessions per day

In summary, in the systemic tolerance studies after inhalation or continuous i.v./s.c. infusion or oral administration, multiples of the intended human dose of Iloprost were tolerated without any symptoms or with minor changes due to the pharmacological effects of the compound. Therefore, on the basis of the results obtained in systemic tolerance studies, no adverse effects are to be expected at the intended human therapeutic inhalative dose.

Reproduction toxicity
The reproductive and developmental toxicity studies performed include fertility and general reproductive performance in male and female rats, embryotoxicity in rats, rabbits, and monkeys, and peri- and postnatal development in rats after continuous i.v. infusion. The oral treatment is documented by a combined study of fertility, reproductive performance, and on embryonic and peri-postnatal development in rats and an embryotoxicity study in rabbits using iloprost clathrate.
In embryo- and foetotoxicity studies in rats, continuous intravenous administration of iloprost led to anomalies of single phalanges of the forepaws in a few foetuses/pups without dose-dependence. These alterations are not considered as true teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to hemodynamic alterations in the fetoplacental unit. In comparable embryotoxicity studies in rabbits and monkeys, no such digit anomalies or other gross-structural abnormalities were observed in the foetuses/pups up to the highest tested dose.
In rats, passage of extremely low levels of iloprost into the milk was observed.
Because of the occurrence of digit anomalies in individual foetuses in reproductive and developmental toxicity studies in the rat, iloprost should not be used in women during pregnancy. Women of childbearing potential should use effective contraceptive measures during treatment. It is not known whether Ventavis enters the breastmilk in humans. The medicinal product must therefore not be administered to breastfeeding mothers. These elements are covered in the SPC and Package Leaflet.

Genotoxicity
All *in vitro* and *in vivo* tests indicate that iloprost is not mutagenic up to cytotoxic concentrations tested. Iloprost is not a gene mutagen in bacterial and mammalian cells *in vitro* and is not clastogenic in human lymphocytes up to cytotoxic concentrations and in the micronucleus test *in vivo*.

Carcinogenicity
In long-term carcinogenicity studies in rats and mice, no drug related neoplastic or non-neoplastic organ toxicity was observed. No tumorigenic potential of iloprost could be demonstrated in tumorigenicity studies in rats and mice.

Local tolerance
In the subacute (4 weeks) and chronic (6 months) inhalation toxicity studies in rats no signs of local irritation in the respiratory tract were observed, even for an iloprost solution with a concentration of 20 µg/ml, which is double the concentration to be used for therapeutics in human patients.

Antigenicity
Studies in guinea-pigs did not reveal any antigenicity and immunotoxicity of iloprost.

Ecotoxicity / environmental risk assessment
The predicted no-effect concentration (PNEC) in water was > 20 µg/l, which means that the estimated occurrence of iloprost in surface waters is of no concern. The potential occurrence in soil is insignificant. The route of administration of iloprost by inhalation does not seem to enhance the environmental risk. Exposure to the environment is considered very limited and no risk of concern would be expected.

Discussion on toxico-pharmacological aspects

Iloprost affects many cell types, including smooth muscle cells, platelets, endothelial vascular cells and mononuclear leucocytes. Some of the main pharmacological actions of iloprost include vasodilatation, preservation of endothelial function, inhibition of platelet aggregation and of monocyte activation. The action of iloprost is very similar to PGI_2, from which it differs mainly in its oral bioavailability and lesser vasodilatory potency.

Iloprost has also been shown to lower pulmonary artery pressure in animal models of pulmonary hypertension. Its potency to inhibit pulmonary vasoconstriction and reduce pulmonary vascular resistance together with platelet anti-aggregatory and antithrombotic activity, effects on vascular remodelling and on endothelial function and inhibition of some aspects of inflammation, seem to be in favour of the proposed therapeutic treatment.

The pharmacological profile of iloprost has been characterised in a number of species under a variety of experimental conditions. For technical reasons, most *in vivo* data have been obtained using intravenous administration of iloprost. Pharmacokinetic data show rapid systemic bioavailability of iloprost following inhalation. After inhalative daily administration in rats iloprost serum concentrations increased reaching C_{max} within 1 to 2 hours. The systemic exposure increased sub-proportionally with increasing the dose (3.6 to 43.7 µg/kg) and proportionally with prolonging the inhalation period (135 to 240 min). Although the inhalation route of administration will provide a better targeting of the drug substance, marked differences in pharmacodynamic responses to iloprost between the systemic and inhalational routes of administration are not expected.

The toxicology programme is mainly based on intravenous, subcutaneous and oral studies in rodent and non-rodent species. The systemic iloprost exposure after parenteral and oral administration exceeds the therapeutic inhalative dose levels in humans.
In acute toxicity studies, single intravenous and oral doses of iloprost caused severe symptoms of intoxication or death at doses about two orders of magnitude above the intravenous therapeutic dose. Considering the high pharmacological potency of iloprost and the absolute doses required for therapeutic purposes, the results obtained in acute toxicity studies do not indicate a risk of acute adverse effects in humans. As expected for a prostacyclin, iloprost produced hemodynamic effects (vasodilatation, reddening of skin, hypotension, inhibition of platelet function, respiratory distress) and general signs of intoxication such as apathy, gait disturbances, and postural changes.

Continuous i.v./s.c. infusion of iloprost up to 26 weeks in rodents and non-rodents did not cause any organ toxicity at dose levels which exceeded the human therapeutic systemic exposure between 14 and 47 times (based on plasma levels). Based on Cmax values in rats, the systemic exposure in these parenteral studies was approximately 3.5 times higher than the maximum achievable exposure after inhalation.

The only studies carried out with inhaled iloprost consist of one subacute toxicity 4 week-study and a chronic toxicity 26 week-study performed in rats. These studies were performed to assess both local tolerance and systemic effects and to provide information on exposure.
The NOAEL are 22,6 µg/kg/day and 48,7 µg/kg/day for the 4-week study and for the 26-week study, respectively. The systemic exposure obtained after a single inhalation session (Cmax = ca. 158 ± 70 pg/mL; AUC ca. 49 pg x h/mL)) is comparable with that obtained after therapeutic continuous intravenous perfusion (135 pg/ml). Based on the results from preclinical inhalation toxicity studies, no deleterious effects precluding the use of inhaled iloprost in humans have been shown. Neither local nor systemic adverse effects were observed after chronic inhaled treatment with a maximum achievable dose, which exceeded the systemic exposure of human patients, achieved by inhalation administration approximately 13 times based on C_{max} values and 127 times based on AUC values.
No signs of toxicity were reported in a repeated dose study in rats (135 minutes/day over 28 days), which mimicked the conditions of inhalatory administration in man. The maximum tolerated dose of iloprost (0.0226 mg/kg/day) was about 25 times that proposed for man (5 µg/ patient i.e. 0.1 µg/kg for a patient of 50 kg body weight for 10 minutes, administered up to 9 times a day).
In the six-month chronic tolerance study in rats exposed to iloprost, doses resulting in plasma levels 13-18 times higher than the human plasma levels found at therapeutic dose (5 µg/patient/session = 158 ± 70 pg/mL at c_{max}), did not cause adverse events.
Iloprost does not appear to be mutagenic or carcinogenic.

The potential adverse events might be due to the exaggerated pharmacological effects of iloprost at the high doses used for the safety animal studies, and thus its therapeutic dosage should be kept under close control and adjusted according to the individual tolerability. Iloprost may potentiate the effects of other vasodilators and anti-thrombotic agents. The tachyphylaxis of platelet inhibitory effects observed during continuous iloprost infusion can be prevented by discontinuing the treatment.

Because of the occurrence of digit anomalies in individual foetuses in reproductive and developmental toxicity studies in the rat, iloprost should not be used during pregnancy in women. No data are

available on the transfer of iloprost to the human milk; a warning on iloprost use in pregnancy and during nursing women is provided in the SPC and Package Leaflet.

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

Iloprost, the active substance of Ventavis, is a synthetic prostacyclin analogue. Iloprost inhibits adenylate cyclase, thus increasing intracellular cyclic AMP levels.

The following pharmacological effects have been observed *in vitro*:

- Inhibition of platelet aggregation, platelet adhesion and release reaction.
- Dilatation of arterioles and venules.
- Increase of capillary density and reduction of increased vascular permeability caused by mediators such as serotonin or histamine in the microcirculation.
- Stimulation of endogenous fibrinolytic potential.

The pharmacological data in humans refers to the dossier provided in support of the Ilomedine Marketing Authorisation Application and published data with inhaled iloprost. No clinical trial data are available for a direct comparison of intra-patient observations of the acute hemodynamic response after intravenous administration to that after inhalation of iloprost.

Acute testing with catheter measurements of pulmonary hemodynamic parameters have shown that after termination of aerosolization, iloprost-induced changes in pulmonary vascular resistance returned to baseline within 60 to 120 minutes while infusion prostacycline (epoprostenol)-induced changes returned to baseline within 10 to 30 minutes. In an acute testing study, increased improvement in arterial oxygenation was observed with inhaled iloprost, and this supports the preferential distribution to well ventilated areas and higher doses of locally deposited prostanoids leading to a probably lower undesirable shunt effect as compared to acute testing with infusion of prostacyclin. However, and alike prostacycline, as the acute response does not in all cases correlate with a long-term benefit of treatment with inhaled iloprost, the predictive value of these acute hemodynamic data are considered to be of limited value for the demonstration of the response and benefit of long-term treatment with inhaled iloprost in patients with pulmonary hypertension. The available pharmacodynamic data does not help to identify responders to the regular treatment with inhaled iloprost. Neither can it be clearly determined whether treatment re-start after discontinuation provides further advantages.
Although *in vitro* studies have shown an effect of iloprost on platelet aggregation, it is not yet proven whether plasma concentrations of inhaled iloprost reach sufficient levels to exert a clinically significant advantage in decreasing the tendency of the blood to clot in patients with pulmonary hypertension similar to that of a conventional anticoagulant. There is no evidence that inhaled iloprost has a significant impact on the disease process through this mechanism.

Pharmacodynamic interaction studies

Two pharmacodynamic drug-drug interaction studies were performed with iloprost via the intravenous route in healthy volunteers. No clinically relevant interactions between iloprost and single dose nifedipine, medinpolol or pentoxifylline were detected during the first study in 12 healthy volunteers. In contrast to the findings in animal studies, the combination of iloprost and captopril had no clinically relevant effect on blood pressure, heart rate and peripheral blood flow in the second study which included 10 healthy volunteers. However, any extrapolation of the results observed in healthy volunteers to patients with pulmonary hypertension would be excessive since they often experience altered and precarious hemodynamic conditions. Moreover, regarding beta-blockers little experience is available in this population since beta-blockers had to be discontinued 4 weeks prior to entry in the clinical study.
Iloprost adds to the effect of vasodilators and antihypertensive agents.

Iloprost can inhibit platelet function and its use with anticoagulants (such as heparin, coumarin-type anticoagulants) or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists: abciximab, eftifibatide and tirofiban) may increase the risk of bleeding. A careful monitoring of the patients taking anticoagulants according to common medical practice is recommended. The concomitant use of other platelet inhibitors should be avoided in patients taking anticoagulants
Intravenous infusion of iloprost has no effect either on the pharmacokinetics of multiple oral doses of digoxin or on the pharmacokinetics of co-administered tissue plasminogen activator (t-PA) in patients.
Although, clinical studies have not been conducted, *in vitro* studies investigating the inhibitory potential of iloprost on the activity of cytochrome P450 enzymes revealed that no relevant inhibition of drug metabolism via these enzymes, or enzyme induction by iloprost have to be expected.

Pharmacokinetics

Several pharmacokinetic studies were performed with iloprost via the intravenous and oral routes of administration. However, only one pharmacokinetic study has been performed with iloprost administered via the inhalation route (study AX15). One of the aims of this study was to compare the plasmatic levels of iloprost when administered with 3 different brands of nebulising devices including those used in the pivotal and the supportive clinical trials. No traditional ADME studies were performed via the inhaled route.

In study AX15, comparing three inhalation devices (HaloLite, Ventstream, Ilo-Neb), a total of 13 patients with pulmonary hypertension (PHT) (iloprost responders), 9 female, 4 male, aged between 26 and 71 years, were treated in a cross over design with a dose of 5 µg iloprost delivered at the mouthpiece. Mean droplet sizes were nearly identical for all devices with only minor differences in the droplet size distribution.
Iloprost serum concentrations were measured by RIA before and at the end of inhalation as well as 2, 5, 15, 30, 60 and 120 minutes thereafter. The pharmacokinetic parameters assessed were C_{max}, Tmax, T1/2 and AUC.

Inhalation Device	Cmax pg/ml	Tmax min	T1/2 Min	AUC pg.h/ml
HaloLite	157 ± 64 (n = 12)	12 ± 5 (n = 12)	7.91 ± 3.16 (n = 11)	47.8 ± 35.2 (n = 12)
Ventstream	155 ± 65 (n = 11)	11 ± 2 (n = 11)	11.3 ± 6.8 (n = 7)	54.2 ± 45.1 (n = 11)
Ilo-Neb	158 ± 70 (n = 12)	12 ± 1 (n = 12)	7.4 ± 2.1 (n = 11)	49.0 ± 34.4 (n = 12)

T1/2: Disposition half-life
AUC: calculated from t=0 until the first sampling time point with C(t) < 25 pg/ml (set to zero for evaluation)

Serum levels reached the limit of detection between 15 and 30 minutes after inhalation, and no second half-life could be calculated.
Similar systemic exposure with iloprost was achieved with all three devices. The ratios of Cmax means and AUC means between treatments were close to unity. However, although containing the value 100%, the confidence intervals are very large (larger than 80-125%) reflecting great variabilities in systemic bioavailability or the low number of patients. Therefore, these plasma level analyses do not allow concluding that “bioequivalence” has been demonstrated between the different devices.

Summary of pharmacokinetic characteristics of different modes of administration

Mode of administration	Single dose	Systemically available dose (% bioavailability)	C_{max} pg/ml	AUC pg.h/ml	Report
Intravenous infusion over 45 min	3ng/kg/min	ca. 9 µg (100%)	135 ± 24	119 ± 34	6210
Oral (immediate release formulation)	1 µg/kg	ca. 14 µg (ca. 20%)	251± 32	144 ± 58	6210
Oral (extended release formulation)	150 µg	ca. 30 µg (ca. 20%)	156 ± 69	313 ± 148	AS07
Inhaled	5 µg	ca. 4 µg (ca. 80%)	157 ± 64	48 ± 35	AX15

AUC: calculated from t=0 until the first sampling time point with C(t) < 25 pg/ml (set to zero for evaluation)

The pharmacokinetic studies performed showed that when iloprost is administered via inhalation in patients with pulmonary hypertension (iloprost dose at the mouthpiece: 5 micrograms), peak serum levels of 100 to 200 picograms/ml were observed at the end of inhalation session. These levels decline with half-lives between approximately 5 and 25 minutes. Within 30 minutes to 1 hour after the end of inhalation, iloprost is not detectable in the central compartment (limit of quantification 25 picograms/ml).
Following intravenous infusion, the apparent steady-state volume of distribution was 0.6 to 0.8 l/kg in healthy subjects. Total plasma protein binding of iloprost is concentration-independent in the range of 30 to 3000 picograms/ml and amounts to approximately 60 %, of which 75 % is due to albumin binding.
Iloprost is extensively metabolised principally via ß-oxidation of the carboxyl side chain. No unchanged substance is eliminated. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form in 4 diastereoisomers. Tetranor-iloprost is pharmacologically inactive as shown in animal experiments. Results of *in vitro* studies reveal that CYP 450-dependent metabolism plays only a minor role in the biotransformation of iloprost. Further in vitro studies suggest that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.
In subjects with normal renal and hepatic function, the disposition of iloprost following intravenous infusion is characterised in most cases by a two-phase profile with mean half-lives of 3 to 5 minutes and 15 to 30 minutes.
A mass-balance study was done using ^{3}H-iloprost in healthy subjects. Following intravenous infusion, the recovery of total radioactivity is 81 %, and the respective recoveries in urine and faeces are 68 % and 12 %. The metabolites are eliminated from plasma and urine in 2 phases, for which half-lives of about 2 and 5 hours (plasma) and 2 and 18 hours (urine) have been calculated**.**

Special groups

In a study with intravenous infusion of iloprost, patients with end-stage renal failure undergoing intermittent dialysis treatment are shown to have a significantly lower clearance (mean CL = 5 ± 2 ml/minute/kg) than that observed in patients with renal failure not undergoing intermittent dialysis treatment (mean CL = 18 ± 2 ml/minute/kg).
Because iloprost is extensively metabolised by the liver, the plasma levels of the active substance are influenced by changes in hepatic function. In an intravenous study, results were obtained involving 8 patients suffering from liver cirrhosis. The mean clearance of iloprost is estimated to be 10 ml/minute/kg**.**
Age and gender are not of clinical relevance to the pharmacokinetics of iloprost.

In vitro nebulisation devices comparison study (A13108)

This study compared the physical features and nebulisation characteristics of 6 nebulisation systems using Ventavis solution. The performance parameters were MMAD, MMD, nebulisation time and dose (µg) of iloprost at mouthpiece. Three jet-nebulisers devices: Prodose, HaloLite, Pari LC Star, and three ultrasonic nebulisers: Optineb, Optineb IR and Multisonic Infracontrol have been investigated. The aerosol output and time of nebulisation were determined by operating the nebuliser on a breath

simulator that was operated with a breath frequency of 15 breaths per minute and a tidal volume of 500ml.

Since the pivotal clinical trial (see discussion on clinical efficacy below) was performed using inhalation either 2.5 µg iloprost in approximately 5 minutes or 5 µg iloprost in approximately 10 minutes, the applicant considered that the suitable nebuliser systems should deliver 2.5µg-5 µg iloprost over approximately 4-10 minutes to enable the bridging between *in vivo* (phase III study) and *in vitro* data.

Based on the results of the new in vitro study, only two jet nebulisers systems reached the above defined criteria and therefore have been recommended in the SPC for use with Ventavis; HaloLite and Prodose (2.5µg disk).

For the dose of 5µg at mouth piece the applicant recommends to complete two inhalations cycles (pre set dose 2.5 µg) with one filling of 2 ml (leading to an inhalation time of 8 to 10 minutes) for both HaloLite and Prodose.

The applicant considers that the tested models of the ultrasonic nebulisers were not appropriate with use of Ventavis since they showed too high output rates (up to 10 µg iloprost at mouthpiece in less than 3 minutes). The applicant considered that not more than 5 µg should be delivered within 4 minutes in order to avoid systemic side effects.
The dose of 5µg could not be reached with LC-Star since only 4.5 µg of iloprost were delivered at mouthpiece at the end of the nebulisation time with one 2 ml ampoule. The dose-nebulisation time relation was not determined and the nebulisation time allowing to deliver 2.5 µg was not established.

Clinical efficacy

The clinical documentation provided to assess the efficacy of inhaled iloprost in the claimed indication consisted of one pivotal study (report RR A02997) and two supportive studies; a phase II study (report RR A00794) for which an interim report was included in the dossier and a pharmacokinetic/hemodynamic study (report RR AX15) designed to compare inhaled iloprost administered with three different nebulising devices. The final report of the phase II study (report RR A02237) was submitted in November 2002. The efficacy data also refers to the experience of iloprost administered via the intravenous route in patients with pulmonary hypertension. The clinical trials were performed according to GCP standards and agreed international ethical principles.

Dose-response studies and main clinical studies:

No formal dose-response study has been conducted with inhaled iloprost. The dosing rationale for the present application and the pivotal clinical study was based on intermediate data from the open labelled study (study A00794**),** publications and internal reports. The phase II study (RR A00794/ A02237) was initiated before the pivotal study (RR A02997) to investigate the appropriate approach to match the individual patient's therapeutic need with tolerability.

The clinical effects observed in the pivotal study (RR A02997) of patients with PHT were achieved with a median daily dose of 30 µg measured at the mouthpiece per day (range: 12.5 to 45 µg delivered at the mouthpiece), corresponding to 6 daily inhalations of 5 µg. More than 80% of patients used this median dose or a higher dose.

The applicant made the assumption that a dose of 2.5 µg or 5 µg delivered at the mouthpiece with a daily inhalation frequency of 6 to 9 to be applied according to the individual patient's needs should allow to cover up to 9-13.5 hours per day during which iloprost improves the pulmonary circulation depending on the duration of the individual pharmacodynamic response. This assumption is based on published data in which the duration of hemodynamic effects after acute testing was 60 to 120 minutes.

Pivotal study (RR A02997)

Description of the study
The pivotal study (RR A02997) was a multicenter, double blind, randomised, 2-arm parallel-group, placebo-controlled study designed to evaluate the safety and efficacy of inhaled iloprost over 12 weeks in adult patients with primary or secondary pulmonary arterial hypertension. Patients were to be stable in NYHA class III or IV for the preceding 4 weeks despite optimal common background therapy comprising anticoagulants, diuretics, digitalis, calcium channel blockers and/or supplemental oxygen. The study treatment was added to the background therapy for pulmonary hypertension. However, patients who had received therapy with prostanoids or prostaglandin such as PGI_1/misoprostol (intravenous only) and PGI_2 (prostacyclin and its analogues) within 6 months of baseline were not to be enrolled into the study. Moreover, betablockers had to be discontinued 4 weeks prior to entry into the study and were not allowed during the study. Patients with new treatment, instable doses of calcium channel blockers within 6 weeks prior to baseline or with critically severe pulmonary hypertension exhibiting signs according to predefined deterioration criteria within the two weeks preceding baseline, were also excluded prior to entry in the study.
Patients with secondary pulmonary hypertension associated with systemic disorders who experienced significant underlying lung disease (i.e. interstitial pulmonary disease, active fibrotic disease, obstructive ventilatory disorders or global respiratory insufficiency) were not included.

Patients were prospectively stratified for pulmonary hypertension origin (i.e. primary or secondary) and for the NYHA class at baseline (III or IV). The patients were randomised within the predefined strata to one of two treatment groups for 12 weeks:
Active treatment - Inhalation of iloprost aerosol with an individually adapted total daily dose of
30 µg at the mouthpiece divided into six equal-dose inhalations of 5 µg. If this dose was tolerated, the total daily dose was to be increased to 45 µg at the mouthpiece divided into nine equal-dose inhalations of 5 µg.
In case of poor tolerability of the single dose of 5 µg at the mouthpiece, the dose was to be reduced to 2.5 µg at the mouthpiece with a total daily dose of 15 µg at the mouthpiece divided into six equal-dose inhalations of 2.5 µg. If this dose was well tolerated, the total daily dose was to be increased to 22.5 µg at the mouthpiece divided into nine equal-dose inhalations of 2.5 µg.
Placebo - Inhalation of a corresponding aerosol placebo to be administered under the same conditions and dosage regimen above.
The inhalation device (nebuliser) used throughout the study was HaloLite.

In total 203 patients (male: 137; female: 66) were randomised (iloprost: n=101; placebo = 102), of whom 120 patients were assigned to NYHA class III (58.6%) and 83 patients to NYHA class IV (41.4%). The baseline 6-minute walk test values reflected a moderate exercise limitation: in the iloprost group the mean was 332 meters (median value: 340 meters) and in the placebo group the mean was 315 meters (median value: 321 meters). 108 patients were diagnosed with primary pulmonary arterial hypertension (PPH) and 95 with secondary pulmonary hypertension (SPH). Among patients with secondary pulmonary hypertension, 56 patients were diagnosed with chronic thromboembolic disease, 34 with connective tissue disease (including CREST and scleroderma) and 4 had secondary pulmonary hypertension associated with appetite suppressant medicinal products.

Randomised patients were between 20 to 70 years of age (mean of age: 52.0 ± 12.6 years old).
The treatment groups were comparable at baseline with regard to age, with the exception to the PPH/ class IV groups where patients tended to be younger in the iloprost group than in the placebo group. In both treatment groups, SPH patients tended to be older than the PPH patients with the SPH/ class IV group showing the highest mean age. The treatment groups were also comparable with regard to weight, height and ethnic origins. The overall female to male ratio was 2:1 as expected for this disease.

RESULTS

Primary efficacy variables:
The primary efficacy objective of the study was based on a composite endpoint consisting of 1) improvement in exercise capacity (6-minute walk test) at 12 weeks by at least 10% versus baseline, and 2) improvement by at least one NYHA class at 12 weeks versus baseline and 3) no deterioration of pulmonary hypertension or death at any time before 12 weeks. For this primary end-point each patient were to be classified as responder or non-responder.
For the combined criteria the walking distance in 6 minutes was measured after the presumed peak plasma level of iloprost (after inhalation). The 6-minute walked distance was also assessed before inhalation of iloprost to measure the trough effect.

17 patients out of 101 in the iloprost group (16.8%) and 5 out of 102 in the placebo group (4.9%) were responders. The difference of responders between the two treatment groups was 12% (p=0.007) and was mainly due to reported changes in NYHA class.
The estimated common odds ratio was 3.97, determined by Mantel-Haenszel inference (95% confidence interval [1.47; 10.75]).
Among the patients with chronic thromboembolic disease (N=56, iloprost group=32 patients; placebo =24 patients) the rate of responders to iloprost was marginal and not statistically different from the placebo group: (iloprost: 4/32 =12,5%; placebo: 2/24=8.3%).

The difference between the two groups in respect of the rate of responders who experienced an improvement in the 6-minute walk test by more than 10% from baseline was low and not statistically significant: 38/101=37.6% in the iloprost group and 26/102=25% in the placebo group (p=0.059).
Overall, 62.4% of patients did not experience an increase over 10% from baseline after 12 weeks of treatment.

	Iloprost (n = 101)		**Placebo (n = 102)**	
Stratum	Responders		Responders	
PPH/III	**5/34**	*14.7%*	**2/36**	*5.6%*
PPH/IV	**6/19**	*31.6%*	**1/19**	*5.3%*
SPH/III	**5/26**	*19.2%*	**2/24**	*8.3%*
SPH/IV	**1/22**	*4.5%*	**0/23**	*0.0%*
All	**17/101**	*16.8%*	**5/102**	*4.9%*

Overview of the components contributing to the combined responder (ITT population)

	Iloprost n = 101	**Placebo n = 102**	**Treatment effect p-value**
Improvement in NYHA class** n [%]	25 (24.8%)	13 (12.7%)	0.032
Improvement of WD of 10% vs. baseline** n [%]	38 (37.6%)	26 (25.5%)	0.059
Deterioration n [%]	5 (4.9%)	9 (8.8%)	0.407
Mortality until week 12 n [%]	1 (1.0%)	4 (3.9%)	0.369

**Component of the primary endpoint. #Values obtained at week 12 after inhalation.
1) Fisher's exact test
2) Stratified Mantel-Haenszel test

Secondary efficacy variables:
An analysis of each component of the combined endpoint has been performed. The secondary efficacy variables studied included: improvement in exercise capacity measured using the 6-minute walk test and ratings of perceived exertion scale (according to Borg scale); improvement in NYHA functional class; improvement in Mahler dyspnea index; improvement in haemodynamic parameters; gas exchange; deterioration of PHT; mortality; need for transplantation; quality of life.

6-minute walk test: The difference between the two groups in respect of the rate of responders who experienced an improvement in the 6-minute walk test by more than 10% from baseline was low and

not statistically significant: 38/101=37.6% in the iloprost group and 26/102=25% in the placebo group (p=0.059).
Overall, 62.4% of patients did not experience an increase over 10% from baseline after 12 weeks of treatment.
The mean value of the absolute change from baseline in 6-minute walking distance observed after 12 weeks of treatment within the overall population included was: 22 meters (-3.3 meters in the placebo group, p=0.032). The Hodges Lehmann estimators for treatment differences (iloprost- placebo) were 20 meters (observed data analysis) and 29 meters (LOCF analysis with the imputation death =0). These values of differences are under the threshold that can be recognised as clinically significant (i.e. 40 meters).

A subgroup analysis showed that there was no treatment effect as compared to placebo with reference to the 6-minute walk test in the subgroup of patients diagnosed with secondary pulmonary hypertension (SPH). In this subgroup, the mean absolute change in 6–minute walk test was –1.8 meters after 12 weeks [–5,1 meters (SPH/class III) and 2,1 meters (SPH/ class IV)] in the iloprost group while the mean change from baseline was +1,5 meters in the placebo group.
A mean increase in the 6-minute walk test of 44.7 meters from a baseline mean value of 329 meters vs. a change of -7.4 meters from a baseline mean value of 324 meters in the placebo group (no data imputation for death or missing values) was observed in the subgroup of 49 patients with primary pulmonary hypertension (PPH) receiving treatment of inhaled iloprost for 12 weeks (46 patients in the placebo group).
After 12 weeks treatment, when the 6-minute walk test was measured at the trough of effect (before inhalation), the mean improvement from baseline was 14,6 meters (median: 16 meters) in the iloprost group; 0,2 meters (median: 0.5 meters) in the placebo group. The mean difference observed between the two groups 14.4 meters was not statistically significant.

Change from baseline in NYHA functional class: With reference to the observed improvement of at least one NYHA functional class, 25/96 (26%) of the patients in the iloprost group and 13/88 (15%) in the placebo group improved (p = 0.032, stratified Mantel-Haenszel test). However, in the iloprost group 65/96 patients (67.7%) remained unchanged and 6/96 patients (6.3%) deteriorated while in the placebo group 67/88 patients (76.1%) remained unchanged and 8/88 patients (9.1%) deteriorated. More patients improved and fewer patients deteriorated with respect to their NYHA functional class in the iloprost group as compared to the placebo group at week 12. This difference was however not statistically significant (Fisher's exact test: p = 0.195).

Improvement in haemodynamic parameters: Invasive haemodynamic parameters were assessed at baseline and after 12 weeks of treatment. The hemodynamic parameters analysed showed significant differences between trough (before inhalation session) and peak (5 minutes after inhalation session) drug effect on pulmonary vascular resistance (PVR: 22% decrease between the two measurements = -211.8 dynxsxcm^{-5} in average p=0.0001) and mean pulmonary artery pressure (mPAP: -8.9 % change between the two measurements = -4.5 mmHg in average, p=0.0001). After 12 weeks the treatment effect, as compared to placebo, was not significant neither in mPAP (p=0.958) nor in PVR (p=0.067) as compared to baseline when these parameters were measured at the trough expected effect (before inhalation).

Other secondary variables: There were no conclusive results with reference to improvement of perceived exertion. The Mahler dyspnea focal scores were comparable for both the active treatment and the placebo groups as well as for PPH and SPH patients.
With respect to deterioration of the disease, there was a tendency in favour of iloprost (fewer iloprost patients developed the defined criteria of deterioration within the 12 weeks of the study). But the difference was not statistically significant between the two groups.
Mortality was low in the two groups, 3 patients died in the iloprost group and 7 in the placebo group.
The results in mortality did not reach statistical significance.
No patient was transplanted during the entire course of the study.
No statistically significant treatment effect was detected using the adapted “Minnesota Living with Heart Failure Questionnaire adapted for PHT” for the evaluation of disease specific QoL in this patient

population. During the study, syncope was reported in 8 of the 101 patients who received iloprost and in 5 of the 102 patients who received placebo (see discussion on clinical safety below).

Dose delivered during study: In the iloprost group, the median inhaled daily dose was at most time points 30 µg divided into 6 inhalations (range: 12.5 µg to 45 µg), and was only slightly higher in the placebo group. The majority of patients inhaled a delivered iloprost dose of 5 µg at the mouthpiece (≥ 80% at all time points). In the iloprost group, the dose and frequency of inhalations did not differ between PPH and SPH groups except for the PPH/ class IV stratum where the median daily dose was increased up to 45 µg in both treatment groups at week 12. As anticipated, about 90% of patients had only inhalations during the day.

Supportive study (interim report RR A00794/ final report RRA02237)

Description of the study:
The supportive clinical trial (RR A00794) was an exploratory, open-label, multicenter, randomised parallel group study comparing the addition of inhaled iloprost to conventional therapy to conventional therapy alone (excluding prostacyclin and analogues and endothelin inhibitors). This study was conducted over three months at the end of which all recruited patients, apart from those who had discontinued treatment due to adverse events or due to deterioration of the pulmonary hypertension, were entered in a second open phase of longer-term iloprost inhalation treatment leading up to 24 months. It was mainly aimed to investigate the safety, tolerability, and clinical efficacy of iloprost inhalation therapy in patients with primary or secondary pulmonary hypertension. Randomization was performed using random permutated blocks within the strata PHT (primary/secondary), calcium antagonist (yes/no), and 6-minute walk (≥ 500 m, 150-499 m, < 150 m). In this study inhalation using 2.8 µg iloprost was delivered at the mouth piece.
This study included a total of 63 patients (from 24 to78 years), all considered clinically stable. 40 patients were diagnosed with primary pulmonary hypertension (iloprost arm: 20 and control arm: 20 during the controlled phase) and 23 patients were diagnosed with secondary arterial pulmonary hypertension (iloprost arm: 10 and control arm: 13 during the controlled phase). Among those with secondary pulmonary hypertension, three patients had chronic tromboembolic disease. Of the 63 patients enrolled, 21 were classified according to NYHA functional class II, 30 to NYHA class III, and 12 to NYHA class IV. Among the 63 patients who were randomised 52 (82.5%) patients continued into the long-term phase and 14 patients discontinued the study during the randomised phase. The interim report of this study where patients had received inhaled iloprost treatment for 9 or 12 months was provided with the dossier. Data from the second year, however, were not yet ready at the time of the submission but were submitted in November 2002 (report RR A02237).

RESULTS

Primary efficacy variables:
Although the study was designed to evaluate safety, a composite response criterion was specified in order to analyse efficacy. Patients were classified as responders if they fulfilled each of the following criteria: No death and improvement in at least one NYHA class and at least a 10 % increase in the 6-minute walking distance from baseline.

TT 13 **Responder rate during randomized phase at month 1, 2 and 3 (unadjusted p-values, Fisher's exact test)**

Week	Iloprost N = 30	Control N = 33	Overall N = 63	Unadjusted p-value
4 (after inhalation)	4	0	4	0.046*
8 (before inhalation)	7	2	9	0.073
12 (before inhalation)	4	0	4	0.046*

*significant (alpha level = 0.05)

Secondary efficacy variables:
Improvement in NYHA functional class; improvement in exercise capacity according to walking distance (6-min walked distance measured either before or within 15 minutes after iloprost inhalation) and Borg scale (rate of perceived symptoms of breathlessness and muscle fatigue at the end of an exercise test); Mahler Dyspnea Index; health-related quality of life; haemodynamic parameters and gas exchange; mortality and lung/heart-lung transplantation.
With reference to improvement in NYHA class, a difference between the treatment groups in favour of iloprost could be found at the time of the analysis, however, not statistically significant (to the 5-% level). During the controlled phase a trend of improvement regarding the 6-minute walk test was observed in favour of inhaled iloprost but the statistical analysis did not show a significant treatment effect. No statistical difference was reached in quality of life assessment and mortality was similar between the two groups within the 3-month controlled phase.

Supportive study (RX15)

Description of the study:
Study RX15 compared the haemodynamic effects and pharmacokinetics in 12 patients with pulmonary hypertension after single doses of nebulised iloprost from 3 brands of nebulising devices Ventstream, the Ilo-Neb system, and the nebulising device used in the pivotal and on-going trials, HaloLite. This was a controlled, randomized, open-label, multicenter, crossover designed study with six sequences, three treatments and three periods. The patients had to be "responders" to inhalation of iloprost aerosol using the Ilo-Neb nebulising device regarding the main target variable, a decrease of pulmonary vascular resistance by at least 20% within 1 hour after inhalation compared to baseline in the last previous right-heart catheter investigation. The mean pulmonary artery pressure (mPAP) must exceed ≧ 30 mmHg. The dose at the mouthpiece was estimated at 5 µg based on *in vitro* characterization of the Ilo-Neb system.

Outcome variables studied:
Change in pulmonary vascular resistance; tolerability as measured by systemic haemodynamic variables; pharmacokinetic evaluation based on individual iloprost levels in serum measured prior to the start and at the end of inhalation as well as 2, 5, 15, 30, 60 and 120 minutes after the end of inhalation.

TT 10 **ANOVA results: maximum percentage change for PVR, simultaneous 95% confidence intervals (CI), multiple significance level = 0.05, adjustment: Tukey-Kramer**

Treatment	vs treatment	maximum percentage change for PVR	adjusted *P*-value	adjusted lower CI limit	adjusted upper CI limit
HaloLite	Ventstream	-0.8%	0.9788	-11.19%	9.58%
Ilo-Neb	Ventstream	-0.6%	0.9881	-10.96%	9.77%
HaloLite	Ilo-Neb	-0.2%	0.9986	-10.59%	10.18%

Statistical significant difference was not observed in the means of the underlying cardiovascular variables (CO, mPAP, PAWP) from which the main target variable, PVR, was derived. *(See also discussion on pharmacokinetics.)*

Clinical studies in special populations
No studies in special patient groups (e.g. in children) were performed.

Discussion on clinical efficacy

Based on the primary efficacy endpoint (prespecified composite criteria: improvement in exercise capacity (6-minute walk test) at 12 weeks by at least 10% versus baseline and improvement by at least one NYHA class at 12 weeks versus baseline and no deterioration of pulmonary hypertension or death at any time before 12 weeks), the overall rate of responders to inhaled iloprost was low (17/101= 16.8%) and was considered mainly due to reported changes in NYHA class. Although this rate was significantly higher than with placebo (5/102=4.9%) (p=0.007), the largest part of patients (i.e. 84/101=83.2%) did not respond to iloprost inhalation therapy according to this combined primary endpoint.

The predefined value of 10% improvement from baseline may not adequately reflect the actual level of improvement of exercise capacity since the definition of “responders” depends on their original baseline value. Hence, this threshold may be reached following a weak improvement in the actual

walking distance in patients with a severe condition and a relatively low baseline value. In any case, these results suggest that 63.4% of patients treated with inhaled iloprost have not experienced an improvement in 6-minute walking distance over 10% from baseline after 12 weeks treatment.
Based on the results on absolute value of the 6-minute walk test the improvement was modest: 22 meters from baseline after 12 weeks of treatment. The estimated treatment effect as compared to placebo was 25.5m (observed cases analysis). When the 6-minute walk test was measured before inhalations the mean change from baseline was not statistically significant as compared to placebo: iloprost: 14.6 ±7.8 meters (median 16 meters); placebo: 0.2 ± 67.3 meters. Consequently, in the largest part of the included population the improvement from baseline in 6-minute walk test was lower than the value of 40 meters, which has been recognised in literature as the threshold of clinical significance in improvement of exercise capacity. In addition, the effect is of short duration (one to two hours) leading to therapeutic gaps compelling patients to frequent nebulisations (6 to 9 per day).

In the pivotal study, a clinically significant improvement in the 6-minute walk test was shown only in the subgroup of patients with primary pulmonary hypertension (PPH). In this subgroup of 95 patients (placebo=46; iloprost=49) the mean treatment effect as compared to placebo on the 6-minute walk test after 12 weeks of treatment was 52.1 m (observed cases analysis, no data imputation). The mean improvement from baseline in the Ventavis group was 44.7 meters (median 31 meters) and the mean change in the placebo group was – 7.4 meters (median 2 meters).

In the predefined subgroup of patients with secondary pulmonary hypertension (placebo: N=48, iloprost N=47) including chronic thrombotic pulmonary hypertension (56/95 patients), drug induced PHT and scleroderma, there was no evidence of efficacy. In this subgroup, based on the primary combined endpoint, most patients (42/48) did not respond to inhaled iloprost (in the placebo group 2/47 patients were classified as responders). Therefore, in the strata of patients with secondary pulmonary hypertension, no treatment effect has been shown regarding exercise improvement. The mean absolute change in 6-minute walk test was – 1.8 meters after 12 weeks in the iloprost group while the mean change was +1,5 in the placebo group; i.e. the mean treatment effect was - 3.3 meters with the observed cases analysis (LOCF with imputation death =0 analysis: mean 6-minute walk test change from baseline in the iloprost group after 12 weeks treatment: -4.2 meters; placebo: -15.7 meters; treatment effect = +11.5 meters). Therefore, no significant treatment effect can be recognised on exercise capacity in this subgroup.

Although the measurement of mPAP and PVR showed a slight non-significant trend of improvement in these parameters in favour of iloprost as compared to the placebo group, no difference was observed between the groups regarding gas exchange (SVO_2). This suggests that the vasodilatory effects measured in the pulmonary artery do not translate in an improvement of respiratory function. As a consequence, the efficacy of this therapy is not established in this patient population. From a pathological point of view, the current classification adopted by the latest consensus (WHO 1998) intended to encompass the fresh knowledge on the treatment and pathogenesis of pulmonary vascular disease clearly separates hypoxic lung disease causing pulmonary hypertension, like chronic thromboembolic disease (including obstruction of proximal and distal pulmonary arteries and *in situ* thrombosis) from the other causes of pulmonary hypertension. Extrapolation from the whole population to this condition would not be appropriate.

Most of the patients included in the pivotal trial who were categorised in NYHA functional class IV, seem to be actually less limited in exercise capacity (as assessed by the 6-minute walk test) than patients with NYHA class IV functional status from other published series or to patients encountered in medical practice. The mean baseline 6-minutes walk test of the inhaled iloprost pivotal study (i.e. 332.4 meters ± 92.8 meters in the inhaled iloprost group) was markedly similar or even higher as compared to the other published comparative studies in which a lower percentage of patients or even no patient were categorised as NYHA class IV functional status. This suggests that different criteria for the assessment of NYHA class IV might have been applied in the pivotal study, resulting in enrolment of less compromised patients. Since the NYHA classification is closely related to the exercise capacity, this suggests that most of the patients included would have been categorised as grade III functional status should they have been assessed according to criteria adopted in other studies or other reference centres. Also, among the pivotal study population the baseline characteristics (6-

minute walk test and pulmonary haemodynamics) were similar in the NYHA class III and class IV subgroups. The similarity of the efficacy results observed in the class III and class IV strata is in line with the similarity in the baseline characteristics of the patients included in these respective strata.
Intravenous prostacyclin is now considered in usual practice and by international consensus as a first line therapy and possibly an alternative to lung transplantation in patients with severe primary pulmonary hypertension. Published reports and clinical experience has shown that intravenous prostacyclin doubles the time on the waiting list for lung transplantation while reducing the risks and improving the outcome of transplantation. Therefore, available data as well as experience in usual practice do not support this benefit with inhaled iloprost.
The small sample size of patients with severe conditions included in the study prevents any assessment of the real impact of inhaled iloprost on exercise capacity and prognosis in the category of patients with the most severe condition as it is encountered in clinical practice.

The long daily time devoted to the nebulisation session due to the high frequency of nebulisations per day (6 to 9 inhalation sessions) will probably favour a risk of non-compliance. Subsequent therapeutic gaps may increase the risk of exertional syncope through increasing pulmonary arterial hypertension induced by modest systemic arterial oxygen desaturation during exercise as well as sleep. This may contribute to a potential deleterious effect of treatment with short duration of effect, especially in patients with advanced pulmonary hypertension.

The criteria for NYHA classification are mostly left to the clinician's discretion and are consequently subject to considerable variability among the investigators. Training was given throughout the studies to investigators and co-investigators by one centrally located NYHA advisor from Shering A.G.
The results observed with respect to this subjective criterion cannot on their own support the benefit of the product in the claimed indication. It should be reminded that strict double blinding might not have been ensured due to the high incidence of visible adverse effects i.e. vasomotor side effects like flushing. At the end of the study, changes in NYHA class accounted for most of the better response rate in the iloprost group as compared with the placebo group. But it cannot be excluded that the assessment procedure might have favoured the assignment to improve categories as the study was going on.

The recommended dose is 2.5 micrograms or 5.0 micrograms of inhaled iloprost (as delivered at the mouthpiece of the nebuliser) according to the individual need and tolerability. The dose per inhalation session should be administered 6 to 9 times per day according to the individual need and tolerability. The duration of treatment depends on clinical status and is left to physician’s discretion. Should patients deteriorate on this treatment intravenous prostacyclin treatment should be considered. Ventavis should only be initiated and monitored by a physician experienced in the treatment of pulmonary hypertension.

In order to define generic performance characteristics for the nebulisers that are commercially available within the EU and that can be recommended for the use of Ventavis, the Applicant has provided an *in vitro* study (A13108) comparing 6 nebulising systems: three compressed air nebulising systems (HaloLite; Prodose; Pari-LC-Star/TurboBoy) and 3 ultrasonic nebulisers (Multisonic Infra Control; Optineb; Optineb volume controlled).

Two compressed air nebuliser systems, HaloLite and Prodose, have been shown to be suitable nebulisers for the administration of Ventavis since the nebulisation characteristics were similar to those of the nebulisation device used in the pivotal study. With both systems the mass median aerodynamic diameter of the aerosol droplet (MMAD) with iloprost was between 2.6 and 2.7 µm. For each inhalation session the content of one 2-ml ampoule of Ventavis will be transferred into the nebuliser medication chamber immediately before use. HaloLite and Prodose are dosimetric systems. They stop automatically after the pre-set dose has been delivered. The inhalation time depends on the patient’s breathing pattern. The efficacy and tolerability of inhaled iloprost when administered with other nebulising systems, which provide different nebulisation characteristics of iloprost solution, have not been established.

It can be concluded that a clinically significant beneficial effect of inhaled iloprost has been observed on exercise capacity only in a restricted part of patients with pulmonary hypertension.
The approved indication is therefore "Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms."
However, the duration of the pivotal trial (12 weeks) was short and the patient population for whom a significant improvement in exercise capacity was observed is small. The Applicant has committed to provide further longer-term safety and efficacy data of Ventavis (iloprost) as part of a post-marketing programme.

Clinical Safety

Patient exposure

The safety database includes a mixture of patients with pulmonary hypertension receiving iloprost via inhaled route and patients receiving iloprost via systemic route (i.e. oral, intravenous) in PHT or other indications (i.e. peripheral arterial occlusive disease). A total of 279 patients with pulmonary hypertension were enrolled in the studies.

The safety data in patients with pulmonary arterial hypertension derived from three clinical trials:

Study no	Total no. patients	Duration of treatment	Median dose and dose range
AX 15 Device comparison study	13	1 day	Delivered dose of 5µg per inhalation at the mouth piece One inhalation with each device
A00794 Phase II study	63 (40 PPH,23 SPH)	Up to 19 months	Nominal daily dose of 100µg (range 50 to 200µg) Divided into 6 inhalation per day (range 3 to 12)
A02297 Phase III study	203 108 PPH, 95 SPH	12 weeks	Delivered daily dose of 30 µg at the mouth piece (range 15 to 45µg) divided into 6 inhalations per day (range 5 to 9)

Furthermore, supportive data are provided for a total of 155 patients with PHT who have been treated with intravenous iloprost and reported in 14 studies. The short-term effect after i.v. iloprost has been investigated in 71 patients in 5 studies. Short-term or acute treatments consist of one or more infusions given over periods of less than one hour.
It is estimated that ilomedin (iloprost iv) has already been used in a significant number of patients worldwide outside of the clinical trials.

Adverse events and serious adverse events/deaths

Study RX 15 – device comparison study:
Vasodilatation was the most frequent event, followed by headache, and cough. Cough and sore throat coincided with the inhalation procedure and could be considered treatment-related. One patient experienced abdominal pain but the time course between administration of the study medication and the occurrence of the AE rules out a causal relationship. There was one case of a supraventricular begiminus, which occurred 39 min after a short inhalation. One patient experienced a mild tachycardia during the 2nd treatment period and a ventricular extrasystole 3 min after a short inhalation. In two patients, the blood pressure decreased by more than 10% as compared to baseline during inhalation.

Study A00794 – Phase II study:

Frequency of Aes	Iloprost (30 patients)	Placebo (33 patients)
> 20%	Vasodilatation Cough	
10-20 %	Chest pain Nausea Headache Trismus	Asthenia Right heart failure Peripheral edema Upper respiratory infection
3-10 %	Back pain Fever Palpitations Diarrhea Syncope Increased creatine phosphokinase Dyspnea hemoptysis hematuria	Back pain Fever Palpitations Diarrhea Syncope

4 patients died during the randomised study phase, 2 in each treatment group. The cause of death was right heart failure.
Five patients in the iloprost group discontinued the study, one due to lack of efficacy, one due to a scheduled lung transplant, three withdrew due to an adverse effect (right heart failure) and four control patients prematurely switched to iloprost aerosol treatment.

Study A02297 – Phase III study:
Incidence of most frequent adverse events (≥10% of patients in the iloprost group) up to week 12:

Event	Iloprost (n=101)	Placebo (n=102)	P value
Cough increased	39 (38.6%)	26 (25.5%)	0.0513
Headache	30 (29.7%)	20 (19.6%)	0.1054
Vasodilatation	27 (26.7%)	9 (8.8%)	0.0009
Flu syndrome	14 (13.9%)	10 (9.8%)	
Peripheral edema	13 (12.9%)	15 (15.7%)	
Nausea	13 (12.9%)	8 (7.8%)	
Trismus	12 (11.9%)	3 (2.9%)	0.0166
Hypotension	11 (10.9%)	6 (5.9%)	0.2163

A higher observed rate in the iloprost group as compared to the placebo group with p-value ($p \leq 0.05$) was found for increased cough, vasodilatation, and trismus.

There were 11 cases of hypotension, 5 of which were considered drug-related. In the placebo group, there were 6 cases of hypotension, 4 of which were considered drug-related. In the iloprost group, serious hypotension occurred in connection with Ca antagonist medication and AV-block in one patient and during the pretreatment catheter test in the other patient. Six of the 11 iloprost patients with hypotension received concomitant vasodilators and diuretics.

There were 39 cases of increased cough, 33 of which were considered drug-related. In the placebo group 26 cases were reported, of which 18 were considered related to the study medication.

Syncope was more frequent in iloprost patients than among patients receiving placebo. Up to week 12, syncope was seen in 8/101 patients in the iloprost group as compared to 5/102 in the placebo group.
The event was reported as a SAE in 5/101 iloprost patients and none in the placebo group (p=0.029). The SAE was assessed as related to the study medication in 3 of 5 iloprost patients.
During the follow-up period, one further patient in either group reported syncope as a SAE. The patient from the placebo group had syncope whilst on treatment with open-label iloprost aerosol.
Syncopes reported in the iloprost group occurred 2 to 9 hour after last inhalation. Three patients experienced syncope after exertion, one patient after getting up in the morning, one patient experienced syncope due to frequent coughing. One patient experienced hypotension and syncope after diuretic medication for oedema. One patient under treatment with a calcium channel blocker

developed AV-block II. No patient had experienced syncope before iloprost treatment and all patients recovered.

Five patients discontinued the study medication in the iloprost group due to adverse events, three due to aggravation reaction, one due to congestive heart failure and one due to cough after inhalation. Eight patients discontinued the study medication in the placebo group due to adverse events, three due to aggravation reaction.
Up to week 12, there was one death in the iloprost group as compared to 4 in the placebo group.
Up to week 16, there were 3 deaths in the iloprost group as compared to 7 in the placebo group. Two of the patients in the placebo group who died between week 12 and week 16 received rescue therapy with prostanoids.
The cause of death were cardiovascular reasons in all but 2 SPH patients with collagenoses for whom death was due to bronchopneumonia/pulmonary fibrosis and respiratory failure due to suspected pneumonia and cardiac arrest, respectively.

Laboratory findings
There were no relevant changes over time for any laboratory parameter in either treatment group with the exception for elevated liver enzymes observed in some iloprost patients in the phase III study (RR A02997). These changes, mostly affecting alkaline phosphatase and gamma-GT, were not considered to be a sign of hepatotoxicity of iloprost, as they were of mild or moderate intensity, did not reach values above three-fold the upper normal limit and were not associated with elevated total bilirubin.
All cases of liver damage were cases of hemodynamic liver stasis. The 2 lab test abnormalities reported as SAEs in the iloprost group are: one patient had an INR increased due to coumarin and the other patient had CK and CK-MB increases of unknown origin.

Safety in special populations
Iloprost elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis. A cautious initial dose titration using dosing intervals of at least 3 hours is recommended. Relevant recommendations have been included in the appropriate sections of the SPC.

Discussion on clinical safety

In the studies provided, death was reported more frequently in the placebo group. Death in the active treatment was not considered related to the study drug.
The adverse effect profile of inhaled iloprost was similar to the one observed with iloprost when administered via other routes and in the other indication (peripheral arterial occlusive disease).
In addition to local effects resulting from administration of iloprost by inhalation such as increased cough, adverse reactions with iloprost are related to the pharmacological properties of prostacyclins. The most common adverse events observed in the clinical studies were headache, jaw pain, nausea, and vasodilation already known from intravenous Ilomedin experience. Trismus with unclear mechanism occurred as a common adverse reactions. Cough was identified as a frequent unknown adverse event and was considered as non-serious in all cases but one where cough lead to discontinuation of iloprost treatment.

Hypotension was reported in 9.2% of patients receiving inhaled iloprost patients as compared with 6.7% of patients in the pooled inhaled placebo groups. In study A02997, hypotension was almost double in the iloprost group (10.9% as compared with 5.9% in the placebo group). In the iloprost group, serious hypotension occurred in 2 cases in connection with calcium antagonist medication and AV-block in one patient and during the pretreatment catheter test in the other patient. In study A02997, 6 of the 11 iloprost patients with hypotension received concomitant vasodilators and diuretics. The occurrence in some patients, of a decline in systemic arterial pressure, suggests that aerosolised iloprost is not purely selective pulmonary vasodilator but rather that there is some systemic spillover of the drug. The systemic vasodilation is closely related to the inhaled dose and the dose delivered at the mouthpiece.
In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic arterial hypotension less than 85 mmHg.

Among serious AEs, syncope was common (7.6% for iloprost combined vs 5.2% for placebo and control combined). In the main controlled study A02997, syncope occurred more frequently in the iloprost group compared with placebo group (5/101 vs 0/102) and this difference was statistically significant. Furthermore, syncope was overall the most frequent serious adverse event. Even though there are confounding factors, investigators considered the AE as drug-related in some cases (3/5 SAE). The patients who experienced syncope had no history of previous syncopes. Syncope is a common symptom of the disease itself, but can also occur under therapy. The increased occurrence of syncopes can be related to the deterioration of the disease or insufficient efficiency of the product. There was no case of discontinuation of study due to syncopal episodes.
The pulmonary vasodilatory effect of inhaled iloprost is of short duration (within one and two hours). Patients who experience syncope in association with pulmonary hypertension should avoid any exceptional straining, for example during physical exertion. Before physical exertion it might be useful to inhale. The occurrence of a nocturnal or exertional syncope reflects therapeutic gaps and/or insufficient efficiency, and the need to adapt and/or change the therapy should be considered.

The AEs related to progression of the disease, i.e. aggravation reaction, dyspnea, congestive heart failure and heart failure, were balanced between treatment groups and there was no hint of a negative effect of iloprost treatment.

Bleeding events (mostly haematoma) were common as expected in this patient population with a high proportion of patients taking anticoagulant co-medication. The frequency of bleeding events did not differ between iloprost and placebo-treated patients.

The use of Ventavis is not recommended in patients with unstable pulmonary hypertension, with advanced right heart failure. In case of deterioration or worsening of right heart failure transfer to other medicinal products should be considered.

In case of interruption of Ventavis therapy, the risk of rebound effect is not formally excluded. Careful monitoring of the patient should be performed, when inhaled iloprost therapy is stopped and an alternative treatment should be considered in critically ill patients.

Overall, during the pivotal studies with inhaled iloprost, only two safety concerns have been raised: cough and syncope, as compared to the safety profile already known with Ilomedin. The safety issues identified have been appropriately addressed in the relevant sections of the SPC and Package Leaflet.
However, it has to be noted that the relevant trials were small and not powered to detect statistically significant differences in side effects. Therefore, the Applicant has committed to provide further longer-term safety and efficacy data for Ventavis (iloprost) as part of a post-marketing programme.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The purity of iloprost active substance, and the control of the manufacturing process and specification for the finished product indicate reliable in vitro reproducibility of this medicinal product. Stability has been shown to be satisfactory; this in turn should indicate a uniform performance in the clinic. There are no unresolved quality issues which could have a negative impact on the benefit / risk balance of the product.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that iloprost has an effect on vasodilatation, preservation of endothelial function, inhibition of platelet aggregation and of monocyte activation. The action of iloprost is very similar to PGI_2, from which it differs mainly in its oral bioavailability and lesser vasodilatory potency. Further, in the general pharmacology studies iloprost was shown to lower pulmonary artery pressure in animal models of pulmonary hypertension. Its potency to inhibit pulmonary vasoconstriction and reduce pulmonary vascular resistance together with platelet anti-aggregatory and antithrombotic activity, as well as its effects on vascular

remodelling, endothelial function and inhibition of some aspects of inflammation, seem to be in favour of the proposed therapeutic treatment.
From the pharmacokinetic point of view, the animal studies performed showed rapid systemic bioavailability of iloprost following inhalation. After inhalative daily administration in rats iloprost serum concentrations increased reaching C_{max} within 1 to 2 hours. The systemic exposure increased sub-proportionally with increasing the dose and proportionally with prolonging the inhalation period.
Overall, the toxicology programme revealed effects as expected for a prostacyclin such as hemodynamic effects (vasodilatation, reddening of skin, hypotension, inhibition of platelet function, respiratory distress) and general signs of intoxication such as apathy, gait disturbances, and postural changes. The therapeutic dosage of iloprost should be kept under close control and adjusted according to the individual tolerability.
Because of the occurrence of digit anomalies in individual foetuses in reproductive and developmental toxicity studies in the rat, iloprost should not be used during pregnancy in women. No data are available on the transfer of iloprost to the human milk; a warning on iloprost use in pregnancy and during nursing women is provided in the SPC and Package Leaflet.

Efficacy

The clinical benefit of Ventavis has been estimated based on the results of the prespecified subgroup analyses of the pivotal phase III study (A02997) that indicated a clinically meaningful improvement in exercise capacity, as evaluated by the 6-minute walk test, in a prespecified subgroup of patients with primary pulmonary hypertension (PPH). After 12 weeks of treatment, the estimated absolute treatment effect in the subgroup of 95 patients with primary pulmonary hypertension (placebo=46; Ventavis =49) on the 6-minutes walk test as compared to placebo, was 52.1 m (observed cases analysis, no data imputation). The mean improvement from baseline in the Ventavis group was 44.7 meters and – 7.4 meters in the placebo group.
Based on the same efficacy criterion, the results were not clinically significant in the subgroup of patients with secondary pulmonary hypertension (SPH) including sclerodermia and chronic thrombotic pulmonary hypertension (CTPH).
Moreover, the baseline characteristics of the patients included with primary pulmonary hypertension prevent any assessment of the real impact of inhaled iloprost in patients with a severe condition as it is encountered in clinical practice in NYHA functional class IV. Further, external data reported that inhaled iloprost has failed to improve the clinical status of patients with a severe condition while many of them were improved with intravenous prostacyclin. Intravenous prostacyclin is now considered in clinical practice and by international consensus as a first line therapy and possibly an alternative to lung transplantation in patients with severe primary pulmonary hypertension.
It can be concluded that a clinically significant beneficial effect of inhaled iloprost has been documented on exercise capacity in a restricted part of patients with pulmonary hypertension.
The approved indication is therefore "Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms."
However, the duration of the pivotal trial (12 weeks) was too short to provide any conclusion on survival and the Applicant has committed to provide further longer-term safety and efficacy data for Ventavis (iloprost) as part of a post-marketing programme.

Safety

The safety data show a relatively mild adverse event profile and reasonable tolerability toVentavis.
In addition to local effects resulting from administration of iloprost by inhalation such as increased cough, adverse reactions with iloprost are related to the pharmacological properties of prostacyclins. The most common adverse events observed in the clinical studies were facial flushing, headache, jaw pain, nausea, bleeding and vasodilation already known from experience with iloprost administered via the i.v. route. Trismus with unclear mechanism occurred as a common adverse reactions. Cough was identified as a frequent unknown adverse event and was considered as non-serious in all cases but one where cough lead to discontinuation of iloprost treatment.
The occurrence in some patients, of a decline in systemic arterial pressure, suggests that aerosolised iloprost is not purely selective pulmonary vasodilator but rather that there is some systemic spillover

of the drug. The systemic vasodilation is closely related to the inhaled dose and the dose delivered at the mouthpiece.
Syncope was overall the most frequent serious adverse event. Increased occurrence of syncopes can be related to the deterioration of the disease or insufficient efficiency of the product. However, there was no case of discontinuation of study due to a syncopal episode. The occurrence of a nocturnal or exertional syncope reflects therapeutic gaps and/or insufficient efficiency, and the need to adapt and/or change the therapy should be considered.
Appropriate recommendations and warnings have been included in the SPC.
The duration of the pivotal trial (12 weeks) was short and the patient population for whom a significant improvement in exercise capacity was observed is small. The Applicant has committed to provide further longer-term safety and efficacy data for Ventavis (iloprost) as part of a post-marketing programme.

Benefit/risk assessment

Following the assessment of the supplementary documentation provided by the applicant, it was concluded that further data was needed to support the safety and efficacy of the product.

At an Oral Explanation before the CPMP, the Applicant focused on the following outstanding issues, as previously defined by the CPMP:

1) The results of the *in vitro* device comparison study should be used to define generic performance characteristics for the nebuliser, which must be included in the SPC and PL, to enable patients to use the product effectively and safely in all European Member States. Moreover, the extrapolation from *in vitro* results for one nebulisation device to clinical effect with another should be justified.

2) The benefit of inhaled iloprost appears to be of questionable clinical relevance. The applicant should discuss the relevance of the effect of the primary endpoint and its composites and define a suitable patient population.

3) The clinical benefit should also be discussed in the light of the short duration of action and the possibility of a rebound effect.

Following the review of the submitted documentation, the responses provided at the oral hearing and the final SPC and letter of undertaking, the CPMP agreed that Ventavis has shown efficacy in patients with primary pulmonary hypertension classified as NYHA functional class III, that is encouraging and possibly clinically relevant and that allows a conclusion on an acceptable benefit/risk despite the limited efficacy and safety data available. The CPMP concluded that a marketing authorisation for Ventavis will be granted under exceptional circumstances, subject to fulfilling the quality follow-up measure and clinical specific obligation undertaken by the Applicant. The indication for which the medicinal product in question is intended is encountered so rarely that the Applicant cannot reasonably be expected to provide comprehensive data on the safety and efficacy of the medicinal product. In order to collect additional data, the applicant has committed to complete a clinical study post-authorisation within pre-specified time frames, the results of which shall form the basis of an annual re-assessment of the benefit/risk profile:

Clinical aspects:

The Applicant will seek Protocol Assistance within 4 months after the final CPMP opinion to discuss an adequate protocol to gather further data on longer-term safety and efficay of Ventavis (iloprost). Progress reports will be provided together with the submission of the PSURs. The first patient will be enrolled within 9 months after adoption of the Protocol Assistance. A final report will be provided within 6 months after last patient completed.

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Ventavis in the treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms, was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.